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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,911	12/08/2006	Xiuyuan Hu	P-IMM 1008US	1623

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,911	HU ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group 1 and SEQ ID NO: 6 in the reply filed on November 13, 2007 is acknowledged. The traversal is on the ground(s) that groups 1 and 2 should be rejoined because the transcript variants of ZPK represented by SEQ ID NOs: 6 and 13 are highly identical, differing only by a 99 nucleotide region that is present in SEQ ID NO: 6 but not in SEQ ID NO: 13. This is found persuasive and these sequences are rejoined.

All claims to non-elected inventions have been canceled. Claims 1-8 and 28-30 are pending and examined on the merits.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 2 depends from claim 1 and recites that the nucleic acid comprises SEQ ID NOs: 6 or 13, however, because this limitation is already required by claim 1, this claim fails to further limit claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites at step b that an increase in a measured level of inhibition indicates an agent inhibits cancer cells, but fails to state what this increase is measured against, rendering the claim indefinite. Claim 28 is indefinite for a similar reason; this claim does not state what the level of down-modulation is measured against.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying inhibitors of ZPK that are agents that inhibit HeLa, DLD-1, AsPC-1 and PC3 cancer cells, does not reasonably provide enablement for identification of ZPK inhibitors as agents that inhibit cancer in other types of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the

state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claims are directed to methods of identifying agents that inhibit cancer cells comprising the steps of introducing an agent that binds SEQ ID NOS: 6 or 13, which encode zipper protein kinase (ZPK), into a cell and measuring the level of inhibition of the cell, where an increase in level indicates the agent inhibits cancer cells. Specific embodiments claimed include the nucleic acid consisting of SEQ ID NOs: 6 or 13, inhibition is measured by an apoptosis or a proliferation assay and in other embodiments the cells are cancerous. In another embodiment the agent down-modulates the RNA correlate of SEQ ID NOs: 6 or 13 and the down modulation is measured using a reporter gene assay.

The claims embrace methods of identifying inhibitors of cancer cells by measuring the effect of an agent on any type of cells, both cancerous and non-cancerous cells, as evidenced by claim 8, which explicitly limits the scope of the claims to cancerous cells.

The specification discloses a correlation between the knockdown of various proteins, as well as the genes and mRNA encoding such proteins, and the treatment of cancer. The specification teaches in example 6 that ZPK has been found to modulate mitogen-activation protein kinase signaling to allow or prevent differentiation and that molecular epidemiological data indicate ZPK is overexpressed in many cancers. The specification provides experimental evidence that ZPK is expressed in experimental cell

lines representing cervical, pancreatic, breast, colon, melanoma and glioma cancers. The specification further teaches that siRNAs targeted to ZPK results in a significant reduction in liquid culture growth of cancer cells, indicating that inhibiting ZPK results in inhibition of both anchorage-dependent and -independent growth of colon, cervical, prostate and breast cancer cells.

The specification does not disclose data regarding inhibition of ZPK in normal (i.e., non-cancerous) cells and does not disclose how one would correlate an observed inhibition of ZPK in these cells with inhibition of this gene in cancerous cells, particularly in view of the specification, which teaches in example 6 that ZPK both allows and prevents differentiation, and the teachings of the prior art that ZPK sometimes increases proliferation and sometimes decreases it.

The claims state that agents that bind and/or down-modulate ZPK inhibit cancer cells by reducing proliferation and increasing apoptosis. The prior art of Germain et al. (US 2004/0053878), however, indicates that inhibition of ZPK does not predictably correlate with inhibition of cancer cells. Germain et al. teaches that ZPK itself prevents cell growth in normal and cancerous cells, teaching at page 7 that murine ZPK expression in keratinocytes induced growth arrest. Murine ZPK has ~85% identity with the human homologue. When ZPK was overexpressed in keratinocytes, these cells were always single in keratinocyte colonies indicating that they did not proliferate at all. Since in this cell line ZPK prevents growth, one of skill in the art would reasonably conclude that inhibiting ZPK in this cell would actually stimulate growth. The effect of ZPK overexpression on three cancer cell lines (A-431, MCF-7 and SW-962) was evaluated by measurement of BrdU incorporation and found to be decreased as

compared to BrdU incorporation when ZPK is not expressed, demonstrating that the expression of kinases such as murine ZPK induces a reduction or a suppression of growth of epithelial cancer cells. This data indicates that inhibition of ZPK in these cancer cells, rather than inhibiting cancer cells, would actually have the opposite effect.

Therefore, because the specification does not teach a correlation between inhibition of ZPK in normal cells providing an effect in inhibiting cancer cells and because the prior art indicates that inhibition of ZPK does not correlate with inhibition of cancer cells in a predictable manner by teaching that ZPK itself prevents cell growth in normal and cancerous cells, the skilled artisan would have to engage in undue, trial and error experimentation to practice the claimed method throughout its full scope. This experimentation would include determining what cancerous cells can be inhibited by inhibiting ZPK, determining what normal cells can be inhibited by inhibiting ZPK and determining a correlation between the normal cells and the cancerous cells that can be inhibited by inhibiting ZPK.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reddy et al. (US 5,554,523) in view of Tritz et al. (US 2004/0248830)

The claims are directed to methods of identifying agents that inhibit cancer cells comprising the steps of introducing an agent that binds SEQ ID NOS: 6 or 13, which encode zipper protein kinase (ZPK), into a cell and measuring the level of inhibition of the cell, where an increase in level indicates the agent inhibits cancer cells. Specific embodiments claimed include the nucleic acid consisting of SEQ ID NOs: 6 or 13, inhibition is measured by an apoptosis or a proliferation assay and in other embodiments the cells are cancerous. In another embodiment the agent down-modulates the RNA correlate of SEQ ID NOs: 6 or 13 and the down modulation is measured using a reporter gene assay.

Reddy et al. disclose the sequence of leucine-zipper protein kinase, ZPK, as SEQ ID NO: 1. Reddy et al. further disclose at column 9 antisense oligonucleotides complementary to SEQ ID NO: 1, which would bind to instant SEQ ID NOs: 6 and 13. Reddy et al. disclose that these oligonucleotides can be administered to neuronal cells in order to inhibit hyperproliferation and that these oligonucleotides can be administered to tumor cells. Reddy et al. do not teach the administration of agents that bind to SEQ ID NO: 6 for the purpose of identifying inhibitors of cancer cells, but does teach step (a) of the claimed method and teaches that this can be done for therapeutic purposes, which necessarily involves measuring the level of inhibition in order to determine efficacy of the treatment.

It was well known to those of ordinary skill in the art at the time the invention was made to screen agents that are able to bind or modulate a gene in cells for the purpose of identifying potential drugs. This routine knowledge is exemplified by Tritz et al., who teach methods of screening for drugs that induce apoptosis. Tritz et al. further teach

assays for measuring the level of apoptosis induced in a cell (see paragraphs 61 and 78-90). These assays include measurement of apoptosis and proliferation and include the use of reporter genes.

It would have been obvious to one of ordinary skill in the art to screen for agents that bind to or modulate ZPK using the screening methods taught by Tritz et al. Based on the teachings of Reddy et al. that ZPK can be inhibited for the purpose of treating cancer, one of ordinary skill in the art would recognize the desirability of identifying ZPK inhibitors and based on the teachings of Tritz et al. of assays to identify compounds that induce apoptosis one would reasonably expect these screening methods to successfully identify agents that inhibit or down-modulate ZPK. While Tritz et al. teach the use of reporter genes in their assays, they do not explicitly recite the specific genes of claim 30, however, one of ordinary skill in the art is aware of numerous reporter genes and recognizes that the reporter genes explicitly claimed could be predictably substituted for those named in Tritz et al. as a matter of design choice in order to use the reporter gene most suitable for a particular assay system.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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